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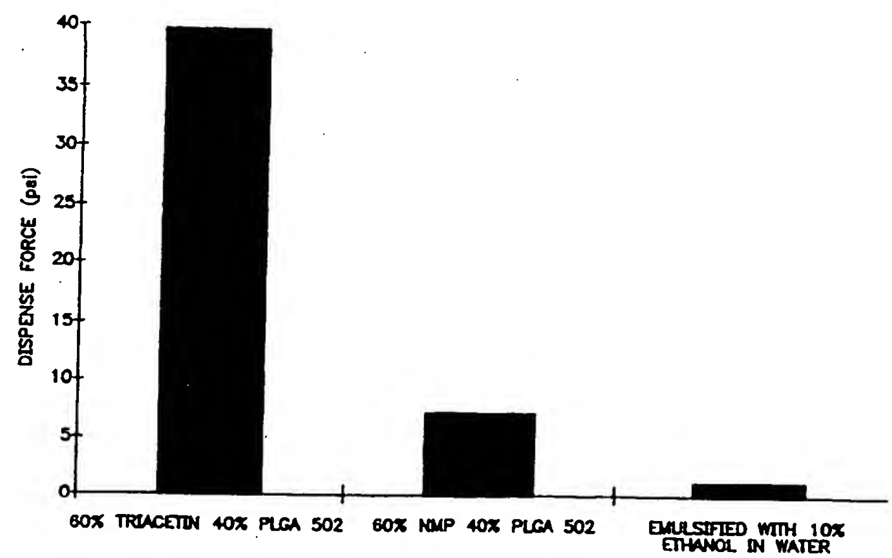


(57) Abstract

An injectable depot gel composition containing a polymer, a solvent that can dissolve the polymer and thereby form a viscous gel, a beneficial agent; and an emulsifying agent in the form of a dispersed droplet phase in the viscous gel. The injectable depot gel composition can be prepared by mixing the polymer and the solvent so that the solvent dissolves the polymer and forms a viscous gel. The beneficial agent is dissolved or dispersed in the viscous gel and the emulsifying agent is mixed with the beneficial agent containing viscous gel. The emulsifying agent forms a dispersed droplet phase in the viscous gel to provide the injectable depot gel composition. The injectable depot gel composition can deliver a beneficial agent to a human or animal with a desired release profile.

# INJECTABLE DEPOT GEL COMPOSITION AND METHOD OF PREPARING THE COMPOSITION

## BACKGROUND OF THE INVENTION

### Field of the Invention

The present invention relates to a depot gel composition that can be injected into a desired location and which can provide sustained release of a beneficial agent. The present invention also relates to a method of preparing the composition.

### Description of the Related Art

Biodegradable polymers have been used for many years in medical applications. Illustrative devices composed of the biodegradable polymers include sutures, surgical clips, staples, implants, and drug delivery systems. The majority of these biodegradable polymers have been based upon glycoside, lactide, caprolactone, and copolymers thereof.

The biodegradable polymers can be thermoplastic materials which means that they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Alternatively, they can be thermosetting materials formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures.

Although thermoplastic and thermosetting biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the bodies of various animals including humans, animals, birds, fish, and

One way to avoid the incision needed to implant drug delivery systems is to inject them as small particles, microspheres, or microcapsules. For example, U.S. Patent No. 5,019,400 describes the preparation of controlled release microspheres via a very low temperature casting process. These materials may or may not contain a drug which can be released into the body. Although these materials can be injected into the body with a syringe, they do not always satisfy the demand for a biodegradable implant. Because they are particulate in nature, they do not form a continuous film or solid implant with the structural integrity needed for certain prostheses. When inserted into certain body cavities such as a mouth, a periodontal pocket, the eye, or the vagina where there is considerable fluid flow, these small particles, microspheres, or microcapsules are poorly retained because of their small size and discontinuous nature. Further, the particles tend to aggregate and thus their behavior is hard to predict. In addition, microspheres or microcapsules prepared from these polymers and containing drugs for release into the body are sometimes difficult to produce on a large scale, and their storage and injection characteristics present problems. Furthermore, one other major limitation of the microcapsule or small-particle system is their lack of reversibility without extensive surgical intervention. That is, if there are complications after they have been injected, it is considerably more difficult to remove them from the body than with solid implants. A still further limitation on microparticles or microcapsulation is the difficulty in encapsulating protein and DNA-based drugs without degradation caused by solvents and temperature extremes.

The art has developed various drug delivery systems in response to the aforementioned challenges. For instance, U.S. Patent No. 4,938,763 and its divisional U.S. Patent No. 5,278,201 relate to a biodegradable polymer for use in providing syringeable, in-situ forming, solid biodegradable implants for animals. In one embodiment, a thermoplastic system is used wherein a non-reactive polymer is dissolved in a biocompatible solvent to form a liquid which is placed in the animal wherein the solvent dissipates to produce the solid implant. Alternatively, a

## SUMMARY OF THE INVENTION

The present invention is a significant advance in the art and in one aspect provides an injectable depot gel composition comprising:

A) a biocompatible polymer;

B) a solvent that dissolves the polymer and forms a viscous gel;

C) a beneficial agent; and

D) an emulsifying agent in the form of a dispersed droplet phase in the viscous gel.

In a further aspect, the present invention provides a method of preparing an injectable depot gel composition comprising:

A) mixing a biocompatible polymer and a solvent whereby the solvent dissolves the polymer and forms a viscous gel;

B) dispersing or dissolving a beneficial agent in the viscous gel to form a beneficial agent containing gel; and

C) mixing an emulsifying agent with the beneficial agent containing gel, said emulsifying agent forming a dispersed droplet phase in the beneficial agent containing gel so as to provide the injectable depot gel composition.

In another aspect, the present invention provides a method of preparing an injectable depot gel composition comprising:

A) mixing a biocompatible polymer and a solvent whereby the solvent dissolves the polymer and forms a viscous gel;

B) dispersing or dissolving a beneficial agent in an emulsifying agent to form a beneficial agent containing emulsifying agent; and

C) mixing the beneficial agent containing emulsifying agent with the viscous gel, said beneficial agent containing emulsifying agent forming a dispersed droplet phase in the viscous gel to provide the injectable depot gel composition.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

As explained above, one aspect of the present invention relates to an injectable depot gel composition comprising:

A) a biocompatible polymer;

B) a solvent that dissolves the biocompatible polymer and forms a viscous gel;

C) a beneficial agent; and

D) an emulsifying agent in the form of a dispersed droplet phase in the viscous gel.

The polymer, solvent and emulsifying agents of the invention must be biocompatible, that is they must not cause irritation or necrosis in the environment of use. The environment of use is a fluid environment and may comprise a subcutaneous or intramuscular portion or body cavity of a human or animal.

Polymers that may be useful in the invention may be biodegradable and may include, but are not limited to polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamines, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and mixtures thereof.

The polymer may be a polylactide, that is, a lactic acid-based polymer that can be based solely on lactic acid or can be a copolymer based on lactic acid and glycolic acid which may include small amounts of other comonomers that do not substantially affect the advantageous results which can be achieved in accordance with the present invention. As used herein, the term "lactic acid" includes the isomers L-lactic acid, D-lactic acid, DL-lactic acid and lactide while the term "glycolic acid" includes glycolide. The polymer may have a monomer ratio of lactic acid/glycolic acid of from about 100:0 to about 15:85, preferably from about

polymer dissolution which leads to greater gel viscosities, with attendant higher force needed to dispense the viscous gel when compared with other solvents. These characteristics enable the beneficial agent to be maintained without exhibiting a burst effect, but make it difficult to dispense the gel through a needle. For instance, as shown in Figure 1, a gel prepared from 40% by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight of triacetin required about 40 psig to dispense the gel through a standard 20 gauge needle at 2 cc/min while a gel prepared from the same amount of polymer with 60% by weight of N-methyl-2-pyrrolidone required only about 8 psig. Figure 1 further shows that when the emulsifying agent (in this case 33% by weight of a 10% ethanol solution) is added to the viscous gel according to the invention, the dispense force needed is only about 2 psig. The shear thinning characteristics of the depot gel compositions of the present invention allow them be readily injected into an animal including humans using standard gauge needles without requiring undue dispensing pressure.

The solvent is typically present in an amount of from about 95 to about 20% by weight and is preferably present in an amount of from about 80 to about 50% by weight and often 65 to 55% by weight of the viscous gel, that is the combined amounts of the polymer and the solvent. The viscous gel formed by mixing the polymer and the solvent typically exhibits a viscosity of from about 1,000 to about 200,000 poise, preferably from about 5 to about 50,000 poise measured at a 1.0 $sec^{-1}$ shear rate and 25° C using a Haake Viscometer at about 1-2 days after mixing is completed. Mixing the polymer with the solvent can be achieved with conventional low shear equipment such as a Ross double planetary mixer for from about 1 to about 2 hours.

The beneficial agent can be any physiologically or pharmacologically active substance or substances optionally in combination with pharmaceutically acceptable carriers and additional ingredients such as antioxidants, stabilizing agents, permeation enhancers, etc. that do not substantially adversely affect the advantageous results that can be attained by the present invention. The beneficial

phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, dexamethasone and its derivatives such as betamethasone, triamcinolone, methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17∝-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, norethiedcrone, progesterone, norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further examples are proteins and peptides which include, but are not limited to, bone morphogenic proteins, insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, somatostatin, lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists, leuprolide, interferons, interleukins, growth hormones such as human growth hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility promoters, growth factors, coagultion factors, human pancreas hormone releasing factor, analogs and derivatives of these

profile that depends more on the degradation of the polymer than the diffusion of the beneficial agent from the composition or vice versa. In this respect, at lower beneficial agent loading rates, one generally obtains a release profile reflecting degradation of the polymer wherein the release rate increases with time. At higher loading rates, one generally obtains a release profile caused by diffusion of the beneficial agent wherein the release rate decreases with time. At intermediate loading rates, one obtains combined release profiles so that if desired, a substantially constant release rate can be attained. While the particular release rate depends on the particular circumstances, such as the beneficial agent to be administered, release rates on the order of from about 1 to about 10 micrograms/day for periods of from about 7 to about 90 days can be obtained. Further, the dose of beneficial agent may be adjusted by adjusting the amount of injectable depot gel injected. As will be apparent from the following results, one can avoid a burst effect and administer on the order of 1% by weight of the beneficial agent in the composition during the first day.

Figure 2 shows the release rates obtained from the compositions described with regard to Figure 1. The gel prepared from 40% by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight triacetin is thick and thus difficult to inject but shows little burst (less than 2% of the beneficial agent is delivered in the first eight days). The gel prepared from 40% by weight of a 50:50 lactic acid:glycolic polymer and 60% by weight N-methyl-2-pyrrolidone is thin and injectable but shows a large burst (greater than 70% of the beneficial agent is delivered in the first eight days). The gel prepared from 27% by weight of a 50:50 lactic acid:glycolic polymer, 40% by weight triacetin and 33% by weight of a 10% ethanol, 90% isotonic saline solution is thin and injectable and shows little burst (less than 10% of the beneficial agent is delivered in the first eight days). In each case, lysozyme is the beneficial agent and comprises 20% by weight of the combined beneficial agent, polymer and solvent formulation.

emulsifying agent and (c) beneficial agent. Prior to use the beneficial agent is mixed with the emulsifying agent, and that solution or suspension is mixed with the polymer/solvent mixture to prepare the injectable depot implant for use.

The emulsifying agent is present in an amount ranging from about 5 to about 80%, preferably from about 20 to about 60% and often 30 to 50% by weight based on the amount of the injectable depot gel composition, that is the combined amounts of polymer, solvent, emulsifying agent and beneficial agent. Illustrative emulsifying agents are water, alcohols, polyols, esters, carboxylic acids, ketones, aldehydes and mixtures thereof. Preferred emulsifying agents are alcohols, propylene glycol, ethylene glycol, glycerol, water, and solutions and mixtures thereof. Especially preferred are water, ethanol, and isopropyl alcohol and solutions and mixtures thereof. The type of emulsifying agent affects the size of the dispersed droplets. For instance, ethanol will provide droplets that have average diameters that can be on the order of ten times larger than the droplets obtained with an isotonic saline solution containing 0.9% by weight of sodium chloride at 21°C.

While normally no other components are present in the composition, to the extent that conventional optional ingredients are desired, such as polyethylene glycol, hydroscopic agents, stabilizing agents and others, they are used in an amount that does not substantially affect the advantageous results which can be attained in accordance with the present invention.

To illustrate various aspects of the invention further, Figure 3 shows the viscosities at different shear rates using water alone and an aqueous mixture containing 10% by volume of ethanol at a weight ratio of 2:1 (gel:emulsifying agent) using a viscous gel formed from 50% by weight of a 50:50 lactic acid:glycolic acid copolymer and 50% by weight of triacetin compared to the viscosities of the viscous gel without emulsifying agent.

It is to be understood that the emulsifying agent of the present invention does not constitute a mere diluent that reduces viscosity by simply decreasing the concentration of the components of the composition. The use of conventional

solution, as an emulsifying agent, in the amount used in Example 1. The emulsifying agent-lysozyme solution is mixed with the amount of gel material used in Example 1 to form an injectable depot gel composition. The fabricated injectable depot gel composition is suitable for injection into an animal.

In accordance with various aspects of the present invention, one or more significant advantages can be obtained. More specifically, using simple processing steps, one can obtain a depot gel composition that can be injected into place in an animal without surgery using a low dispensing force through standard needles. Once in place, the composition will quickly return to its original viscosity and may exhibit rapid hardening so as to substantially avoid a burst effect and provide the desired beneficial agent release profile. Furthermore, once the beneficial agent has been fully administered, there is no need to remove the composition since it is fully biodegradable. As a still further advantage, the present invention avoids the use of microparticle or microcapsulation techniques which can degrade certain beneficial agents, like peptide and nucleic acid-based drugs and which microparticles and microcapsules maybe difficult to remove from the environment of use. Since the viscous gel is formed without the need for water, temperature extremes, or other solvents, suspended particles of beneficial agent remain dry and in their original configuration, which contributes to the stability of thereof. Further, since a mass is formed, the injectable depot gel composition may be retrieved from the environment of use if desired.

The above-described exemplary embodiments are intended to be illustrative in all respects, rather than restrictive, of the present invention. Thus the present invention is capable of many variations in detailed implementation that can be derived from the description contained herein by a person skilled in the art. All such variations and modifications are considered to be within the scope and spirit of the present invention as defined by the following claims.

4. The injectable depot gel composition of claim 3 wherein the lactic acid-based polymer has a monomer ratio of lactic acid to glycolic acid in the range of 100:0 to about 15:85.

5. The injectable depot gel composition of claim 3 wherein the lactic acid-based polymer has a number average molecular weight of from 1,000 to 120,000.

6. The injectable depot gel composition of claim 1 wherein the solvent that can dissolve the biocompatible polymer to form a viscous gel is selected from the group consisting of triacetin, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol formal, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacyclo-heptan-2-one and mixtures thereof.

7. The injectable depot gel composition of claim 1 wherein the solvent is selected from the group consisting of triacetin and N-methyl-2-pyrrolidone, and mixtures thereof.

8. The injectable depot gel composition of claim 1 wherein the solvent is triacetin.

16. The injectable depot gel composition of claim 1 wherein the beneficial agent is present in an amount of from 1 to 50% by weight of the combined amounts of the polymer, the solvent and the beneficial agent.

17. The injectable depot gel composition of claim 1 wherein the beneficial agent is in the form of particles dispersed or dissolved in the viscous gel.

18. The injectable depot gel composition of claim 17 wherein the beneficial agent is in the form of particles having an average particle size of from 0.1 to 100 microns.

19. The injectable depot gel composition of claim 1 wherein the emulsifying agent is selected from the group consisting of water, alcohols, polyols, esters, carboxylic acids, ketones, aldehydes and mixtures thereof.

20. The injectable depot gel composition of claim 1 wherein the emulsifying agent is selected from the group consisting of alcohols, propylene glycol, ethylene glycol, glycerol, water and solutions and mixtures thereof.

21. The injectable depot gel composition of claim 1 wherein the emulsifying agent is selected from the group consisting of ethanol, isopropyl alcohol, water, solutions thereof, and mixtures thereof.

C) mixing the beneficial agent containing emulsifying agent with the viscous gel, said beneficial agent containing emulsifying agent forming a dispersed droplet phase in the viscous gel to provide the injectable depot composition.

26. An injectable depot gel composition comprising:

A) a biocompatible polymer;

B) a solvent that dissolves the polymer and forms a viscous gel; and

C) an emulsifying agent in the form of a dispersed droplet phase in the viscous gel.

27. A kit adapted to provide an injectable depot composition comprising as kit components: (a) a biocompatible polymer and a solvent that dissolves the polymer and forms a viscous gel; (b) emulsifying agent; and (c) beneficial agent.

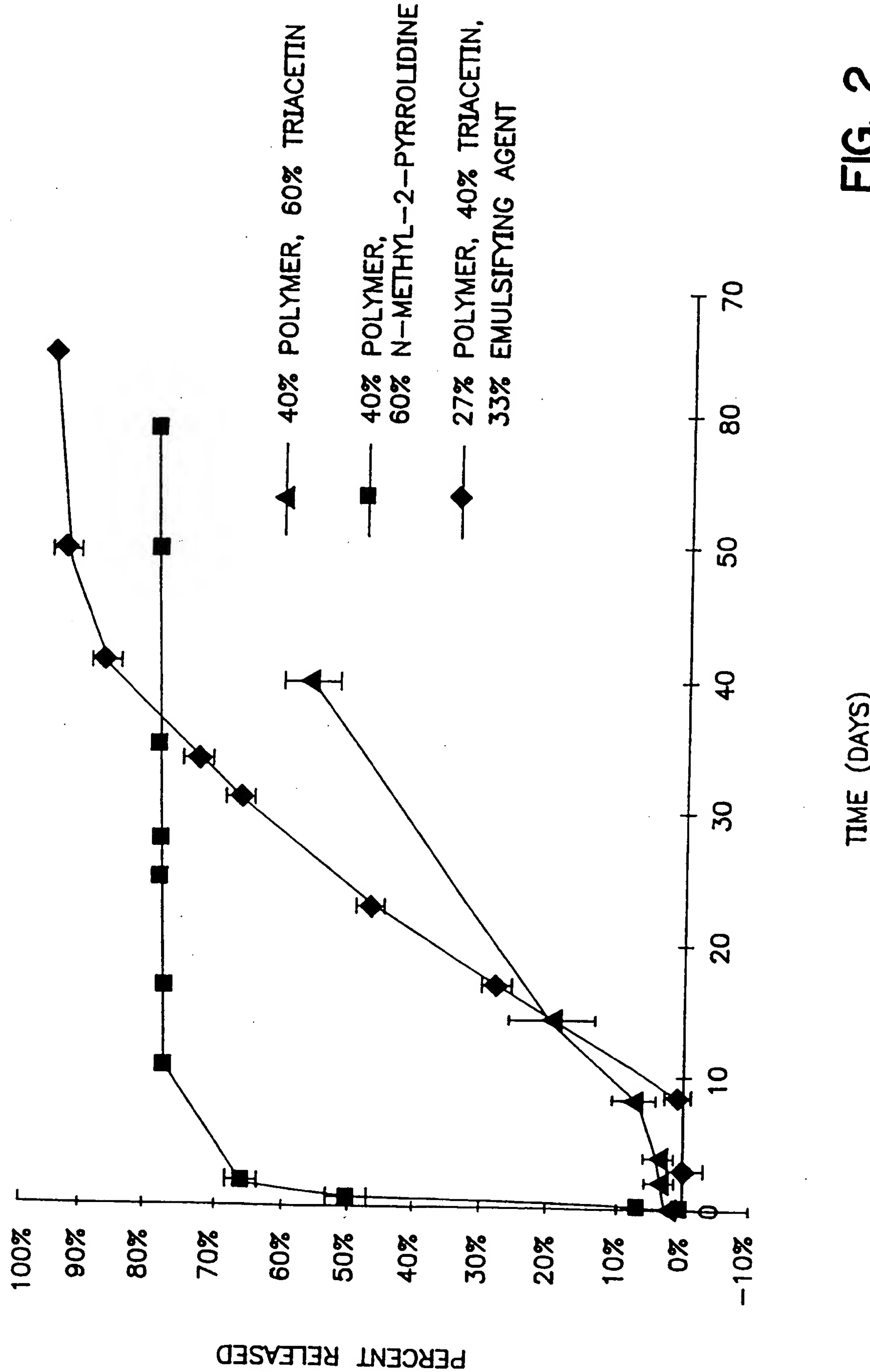
40% POLYMER, 60% TRIACETIN
40% POLYMER, 60% N-METHYL-2-PYRROLIDINE
27% POLYMER, 40% TRIACETIN, 33% EMULSIFYING AGENT
PERCENT RELEASED
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
-10%
0
10
20
30
40
50
60
70
TIME (DAYS)

FIG. 2